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COMMUNICATION

Pd(II)-Catalyzed Controllable C−H Mono-/Diarylation of Aryl Tetrazoles: Concise Synthesis of Losartan

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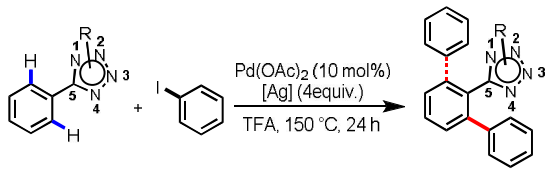
A palladium(II)-catalyzed C–H arylation directed by tetrazole, a metabolically stable surrogate for the carboxylic acid group in drug design, has been developed. Excellent mono-/di-selectivity was achieved through the protecting site adjustment on tetrazole ring. The synthetic utility of this new transformation was demonstrated in the concise total synthesis of Losartan.

With the rapid development in the past two decades, transition-metal-catalyzed direct C–H functionalization has emerged as a potential valuable tool in the total synthesis of natural products and drugs due to its atom-economy and step-economy.[1] To address the inert nature of C–H bonds and the requirement of site selectivity control, directing groups were introduced to direct the catalysts to active the desired C–H bonds by coordination with the metal centers.[2] While a variety of directing groups were successfully used in direct C–H functionalizations with different transition metals,[2] the additional installing and removing steps of such ligands remarkably limited the application of this strategy. One good solution is to utilize the functional groups available in the target molecules or key intermediates as directing groups.

The tetrazole, commonly known as a bioisostere of carboxylic acid moiety, served as a metabolically stable surrogate for the carboxyl functionality in drug design.[3] Many biologicly active aromatics, including the highly commercially succesful Losartan and Valsartan, was dramatically improved in both binding affinity and oral bioavailability. To the best of our knowledge, such tetrazoles have been less studied in direct C–H functionalizations catalyzed by transtion metal,[4,5] especially for palladium catalyst.[5] Within our continous efforts to develop synthetic useful C–H functionalization methods towards total synthesis of complex molecules,[6] we herein report a controllable mono/diarylation of aryl tetrazoles through palladium-catalyzed C–H activation,[7] whose synthetic potential is illustrated by application in the concise total synthesis of Losartan from commercially available starting materials.[4g]

Table 1 Pd-catalyzed controllable C–H mono-/diarylation: optimization of reaction conditions [a,b]



1a: R = 1-Bn
2a: R = 2-Bn

3a

4a (mono): R = 1-Bn
5a (di): R = 2-Bn

entry	substrate	Ag salt	PhI (eq.)	conc. (M)	yield (%)[b]
1	**1a**	Ag_2CO_3	8	2.0	**4a**, 48
2	**1a**	Ag_2CO_3	8	1.0	**4a**, 65
3	**1a**	Ag_2CO_3	8	0.5	**4a**, 52
4	**1a**	AgOAc	8	1.0	**4a**, 70
5	**1a**	Ag_2O	8	1.0	**4a**, 63
6	**1a**	AgOAc	4	1.0	**4a**, 42
7	**1a**	AgOAc	2	1.0	**4a**, 32
8	**1a**	AgOAc	10	1.0	**4a**, 76
9[c]	**1a**	AgOAc	10	1.0	**4a**, 85
10[d]	**1a**	AgOAc	10	1.0	0
11	**1a**	-	10	1.0	**4a**, trace
12[e]	**1a**	AgOAc	10	-	**4a**, 35
13[f]	**2a**	AgOAc	10	1.0	**5a**, 96
14[f,g]	**2a**	AgOAc	10	1.0	**5a**, 23

[a] Conditions: **1a** or **2a** (0.2 mmol, 1.0 equiv), $Pd(OAc)_2$ (10 mol%), silver salt (4.0 equiv), TFA, 150 °C, 24 h. [b] Isolated yield of monoarylation product. [c] $Pd(OAc)_2$ (5 mol%) was used. [d] Without $Pd(OAc)_2$. [e] In the absence of TFA. [f] $Pd(OAc)_2$ (15 mol%) was used. [g] PhBr was used instead of PhI.

We commenced our study with 1-benzyl-5-phenyl-1*H*-tetrazole (**1a**) as the pilot substrate in the presence of $Pd(OAc)_2$ (10 mol%) and AgOAc (4 equiv.) in trifluoroacetic acid (TFA) at 150 °C for 24 hours in sealed tube. To our delight, only monophenylation product **4a** was obtained at 48% yield, presumably due to the steric hindrance of 1-benzyl group, with 8 equiv iodobenzene used. (entry 1, Table 1). The careful examination of concentration indicated 1.0 M was optimal (entries 2-3). Survey of silver species was next undertaken, which

showed AgOAc gave the best result (entries 4-5). To further improve the yield, investigation of the amount of iodobenzene was carried out, affording slightly higher yield with the addition of 10 equiv. of PhI (entries 6-8). To our satisfactory, the decrease of the catalyst loading to 5 mol% gave even the best yield to 85% (entry 9). Lastly, control experiments demonstrated no desired product was generated without $Pd(OAc)_2$ as catalyst (entry 10), and the yield would be only trace or significantly reduced without Ag or TFA (entries 11-12). Notably, only diphenylation product **5a** was obtained at excellent yield (96%) by changing the protecting site of benzyl group from 1- to 2-position on tetrazole ring (entry 13). Additionally, only 23% yield of **5a** was afforded when PhBr was used instead of PhI.

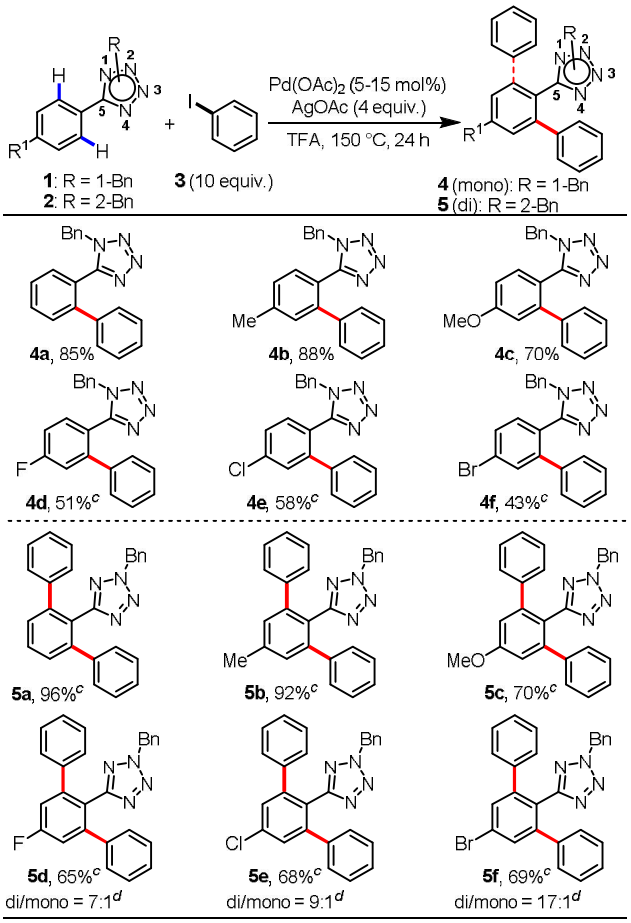


Fig. 1 Controllable mono-/diarylation of aryltetrazoles. [a] Conditions: **1** or **2** (0.2 mmol, 1.0 equiv), **3a** (10.0 equiv), $Pd(OAc)_2$ (5 mol%), AgOAc (4.0 equiv), TFA (0.2 mL), 150 °C, 24 h. [b] Isolated yield. [c] $Pd(OAc)_2$ (15 mol%) was used. [d] Determined by ^1H NMR analysis of crude products.

With the optimized reaction conditions in hand, we set out to investigate the substrate scope for the controllable mono-/diarylation of tetrazoles **1** and **2**. A variety of *para*-substituted aryltetrazoles were arylated smoothly with iodobenzene to give the corresponding coupling products **4** or **5** in modest to excellent yield (up to 96%, Table 2). As for the 1-benzyl protecting *para*-substitued aryl tetrazoles **1**, only monoarylation products were obtained with moderate to good yields. On the other hand, 2-benzyl protecting aryl tetrazoles **2** with both electon-donating and electron-withdraing substituents afforded the diarylation tetrazoles, albeit with minor monoarylation products for the latter substrates.

Subsequently, we further investigated the generatity for the arylation of *ortho*- and *meta*-subsituted aryltetrazoles. While the *ortho*-substitued 1-benzyl aryltetrazoles **1** gave almost none of the desire products, presumably due to the steric hindrance effect, 2-benzyl aryltetrazoles **2** were arylated smoothly to produce the corresponding biaryl tetrazole with good to excellent yields. Additionally, 2-benzyl aryltetrazoles **2** showed also higher reactivity even for the *meta*-substituted tetrazoles, compared with the 1-benzyl substrates **1**. Not only electon-donating groups, such as MeO, Me, but also weak electron-withdrawing groups, such as F, Cl, Br, were well tolerated in our new catalytic system. Notably, heterocycle substrate was also compatible with this method at acceptable yield (**4q**). We next set out to examine the substuent efffect of iodobenzene, which showed the *ortho*- and *meta*-substituted iodobenzenes, including both electron-rich and electron-deficient substituents, coupled with phenyltetrazoles pretty well with good yields. Of particular note is, the presence of halogen atoms at both aryl rings of the products **4** offered potential synthetic elaboration *via* transition metal-catalyzed cross coupling reactions.

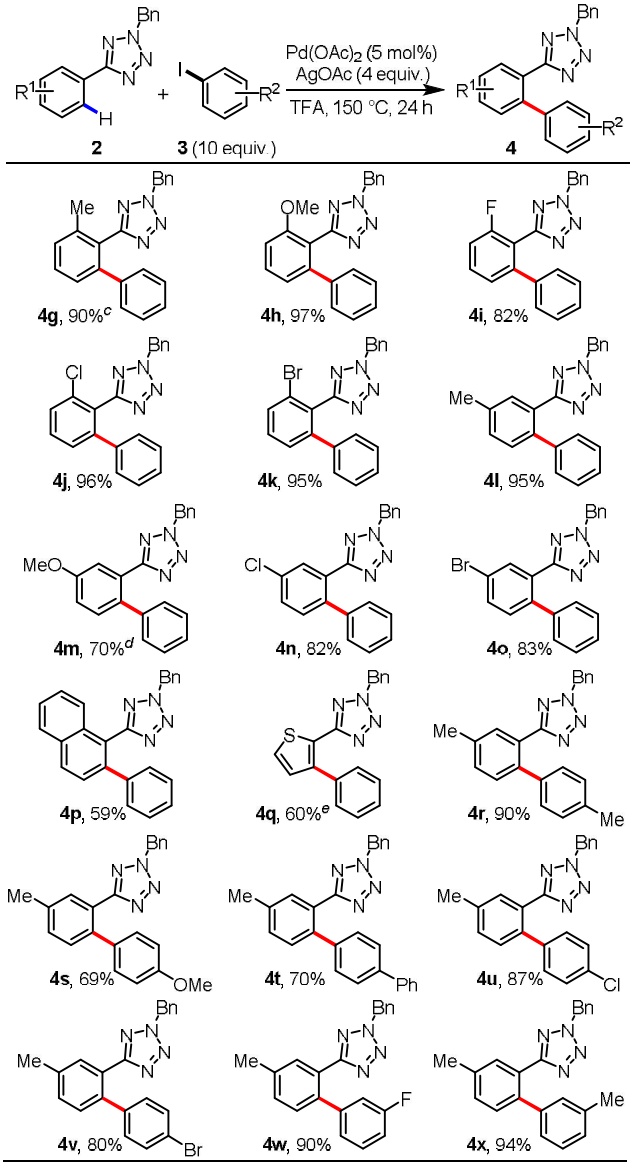
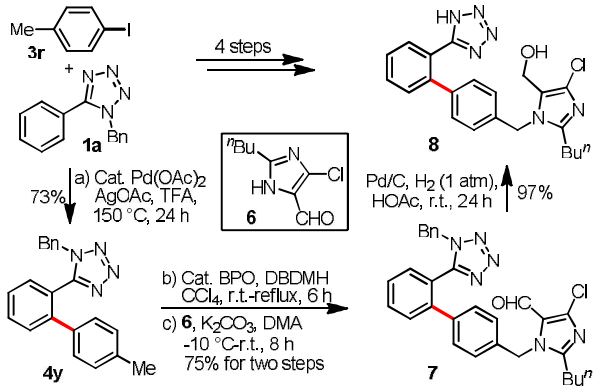


Fig. 2 Monoarylation of 2-benzyl aryltetroazoles. [a] Conditions: **2** (0.2 mmol, 1.0 equiv), **3** (10.0 equiv), $Pd(OAc)_2$ (5 mol%), AgOAc (4.0 equiv), TFA (0.2 mL), 150 °C, 24 h. [b] Isolated yield [c] 140 °C. [d] 130 °C. [e] 120 °C.

To demonstrate the synthetic potential of this new method, we next carried out a concise total synthesis of Losartan, an angiotensin II receptor antagonist drug used to treat hypertension, with our newly developed C–H monoarylation as key step. Whereas previous

synthetic route used relatively complex starting materials prepared *via* several steps,[4g] our synthetic strategy is comparatively straightforward from commercially available 4-iodotoluene (Scheme 1). The monophenylation of tetrazole **1a** with 4-iodotoluene **3r** under optimized reaction conditions [$Pd(OAc)_2$ (5 mol %)] gave the biphenyl tetrazole **4y** in 73% yield, which was subsequently bromined with DBDMH (1,3-dibromo-5,5-dimethyl hydantoin) using the BPO as the radical initiator and then substituted *via* nucleophilic attack of imidazole-5-carbaldehyde **6** to afford the biphenyl tetrazole **7** (75%) in one-pot.[8] Finally, Losartan was obtained after the simultaneous deprotection of *N*-benzyl group and reduction of the formyl group of **7** under 1 atm H_2 atmosphere in the presence of 10% Pd/C.[9]



Scheme 1 Total synthesis of Losartan

In summary, we have developed the first example of tetrazole-directed Pd(II)-catalyzed C–H arylation. Excellent mono-/di-selectivity was achieved through the adjustment of the protecting site on tetrazole ring. The synthetic potencial of this new transformation was demonstrated by the concise total synthese of Losartan from commercially available starting materials. Additional work to test this methodology in other synthetic utility is currently underway in our laboratory.

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Notes and references

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